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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,132	02/23/2007	John W. Adams	AREN-060 (060.US2.PCT)	9424

65643 7590 06/01/2009

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EXAMINER	
LI, RUIXIANG	

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
06/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,132	ADAMS ET AL.	
	Examiner	Art Unit	
	RUIXIANG LI	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *136-157* is/are pending in the application.

4a) Of the above claim(s) *144-154* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *136-143 and 155-157* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/25/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence alignment* .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 136-143 and 155-157) and species hypertrophic cardiomyopathy in the reply filed on 03/06/2009 is acknowledged. The traversal is on the ground(s) that the claims are linked by a single inventive concept, namely the link between RUP40 (SEQ ID NO: 2) and cardiovascular disease. Applicants argue that since the link between RUP40 (SEQ ID NO: 2) and cardiovascular disease is reflected in all of the claims 136-154, the requirement of PCT Rule 13.1 have been met and the restriction requirement should be withdrawn. This is not found to be persuasive for the reasons set forth on pages 3-5 of the previous office action mailed on 09/09/2008).

   The requirement is still deemed proper and is therefore made FINAL.

2. Applicants amendment filed on 03/06/2008 has been entered. Claims 136-157 are pending. Claims 136-143 and 155-157 are currently under consideration. All other claims are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made wit traverse in the reply filed on 03/06/2009.

Information Disclosure Statement

3. The information disclosure statement filed on 05/25/2006 has been considered by the examiner.

Drawings

4. The specification refers to drawings (see, e.g., page 67). However, the drawings are not on the record.

Claim Rejections—35 USC § 112, 1st paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 136-143 and 155-157 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. Possession may be shown, for example, by describing an actual reduction to practice of the claimed invention. A specification may describe an actual reduction to practice by showing that the inventor constructed an embodiment or performed a process that met all the limitations of the claim and determined that the invention would work for its intended purpose.

It is not the case here. Claims 136-143 and 155-157 are drawn to a method comprising (a) contacting a candidate compound with a G protein-coupled receptor

comprising an amino acid sequence having at least 95% identity to amino acids 991 to 1346 of SEQ ID NO: 2, wherein said GPCR is present on a cell or isolated membrane thereof; (b) determining the ability of the compound to modulate the G protein-coupled receptor; and (c) determining if said compound has an activity that inhibits hypertrophy in heart. Since there is no nexus between (b) and (c), the claims, as written, encompass two unrelated methods: determining the ability of a compound to modulate the G protein-coupled receptor and determining if a compound has an activity that inhibits hypertrophy in heart. The instant disclosure fails to describe an actual reduction to practice of the claimed invention. There is no showing that the inventor constructed an embodiment or performed a process that met all the limitations of the claim and determined that the invention would work for its intended purpose. Accordingly, one skilled in the art would not recognize from the disclosure that the Applicants were in possession of the claimed methods at the time the application was filed.

7. Claims 136-143 and 155-157 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

The factors that are considered when determining whether a disclosure satisfies enablement requirement include: (i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of

working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (Bd Pat. App. & Int. 1986); *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claims 136-143 and 155-157 are drawn to a method comprising contacting a candidate compound with a G protein-coupled receptor comprising an amino acid sequence having at least 95% identity to amino acids 991 to 1346 of SEQ ID NO: 2, determining the ability of the compound to modulates said G protein-coupled receptor, and determining if said compound has an activity that inhibits hypertrophy in heart. The claims encompass a method of using a genus of GPCR polypeptides comprising an amino acid sequence having at least 95% identity to amino acids 991 to 1346 of SEQ ID NO: 2. The claims do not require that GPCR variants or homologues possess any particular biological activity, nor any particular conserved structure, nor other disclosed distinguishing feature. Moreover, since there is no nexus between (b) and (c), the claims, as written, encompass two unrelated methods: determining the ability of a compound to modulate the G protein-coupled receptor and determining if a compound has an activity that inhibits hypertrophy in heart. Thus, the claims are overly broad.

The specification discloses the human RUP40 GPCR polypeptides set forth in SEQ ID NO: 2 and the nucleic acid sequence of SEQ ID NO: 1 encoding the polypeptide. The specification also discloses two orthologs of human RUP40, rat RUP40 and mouse RUP40 (see, e.g., paragraph [0038]). The specification asserts

that RUP40 is highly expressed in heart, lung, aorta and adipose (page 68, paragraph [0320]) and that over-expression of RUP40 in cardiomyocytes result in increased IP3 accumulation (Example 14) and a subsequent increase in atrial natriuretic factor (ANF) expression and hypertrophy (page 13, paragraph [0016]; Example 15).

However, the specification fails to provide sufficient guidance and/or working examples with respect to how to make and use the claimed invention. The specification fails to disclose a biological ligand or an active agonist that activates the human RUP40 set forth in SEQ IUD NO: 2. Moreover, the human RUP40 is not disclosed as being constitutive active. Without a known ligand/agonist, one skilled in the art would not be able to identify an antagonist of the human RUP40 that inhibits hypertrophy in heart.

The specification asserts that three variants of human RUP40 of SEQ ID NO: 2 were envisioned (page 15, paragraph [0056]). However, there is no description of other mutational sites that exist in nature, and there is no description of how the structure of the polypeptide of SEQ ID NO: 2 relates to the structure of different variants. The general knowledge in the art concerning variants does not provide any indication of how the structure of one variant is representative of other unknown variants having concordant or discordant functions. The nature of variants is such that they are variant structures where the structure and function of one does not provide guidance to the structure and function of others.

The prior art (see, e.g., U.S. Patent No. 7,049,096) teaches a human GPCR,

which comprises amino acids 991 to 1346 of SEQ ID NO: 2 (see attached sequence alignment). However, the prior art does not teach the ligand of the human RUP40 and does not provide compensatory structural or correlative teachings to enable one skilled in the art to make the encompassed GPCR variants and homologues that can be used in the instant claimed method.

It is unpredictable whether a GPCR that has 95% sequence identity to SEQ ID NO: 2 shares the same property of RUP40 GPCR of SEQ ID NO: 2 because the instant disclosure fails to provide sufficient description information, such as definitive structural or functional features of the recited genus of GPCR variants and homologues. There is no description of the conserved regions that are critical to the structure and function of the genus recited. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. It would take undue experimentation for one skilled in the art to practice the instantly claimed invention.

Finally, it is pointed out that step (b) of claim 136 recites "determining the ability of the compound to modulate said G protein-coupled receptor". A modulator can be either an agonist or an antagonist (see, e.g., paragraph [0364]). If an antagonist of the RUP40 receptor inhibits hypertrophy in the heart as recited in claim 136, an activator (agonist) of the receptor would not be able to inhibit hypertrophy in the heart.

Accordingly, in view of the various factors, the instant disclosure fails to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

Claim Rejections—35 USC§ 112, 2nd paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 136-143 and 155-157 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 136-143 and 155-157 are indefinite because the claims do not have a preamble and the steps set forth in the methods are so ambiguous that they fail to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 136 is indefinite because it recites "determining the ability of the compound to modulate said G protein-coupled receptor". It is unclear what is to be modulated, rendering the claim indefinite.

Claim 136 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how to determine the

ability of a compound to modulate the G protein-coupled receptor; and how to determine is said compound has an activity that inhibits hypertrophy in the heart.

Claim 155 is indefinite because claim 136, from which claim 155 depends, recites "determining if said compound has an activity that inhibits hypertrophy in the heart", whereas claim 155 recites "determining whether said compound modulates cardiomyocyte hypertrophy in said mammal". It is noted that the term "modulates" includes both "inhibits" and "enhances" (see, e.g., paragraph [0364] of the instant specification). If an inhibitor of the receptor inhibits hypertrophy in the heart as recited in claim 136, an activator of the receptor would not be able to inhibit hypertrophy in the heart.

Claim Objections—Minor Informalities

10. Claims 136-143 and 155-157 are objected to because they recite non-elected species (species other than hypertrophic cardiomyopathy). Appropriate correction is required.

Conclusion

11. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875.

The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

/Ruixiang Li/
Primary Examiner, Art Unit 1646

May 23, 2009